CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

5-HYDROXYMETHOXYMETHYL-1-AZA-3,7-DIOXABICYCLO(3.3.0) OCTANES

Chemical Code # 1965, 1966, 1967, Tolerance # 50290, 51922
SB 950 # 109, 706 and 707

March 27, 1992
Revised July 7, 2003

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file
Subchronic, rat (drinking water)	Data gap, inadequate study, no adverse effect indicated
Subchronic, rabbit dermal	Data gap, inadequate study, no adverse effect other than dermal irritation
Chronic toxicity, dog:	Data gap, no study on file
Oncogenicity, rat:	Data gap, no study on file
Oncogenicity, mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	No data gap, no adverse effect (other than dermal irritation)
Teratology, rabbit:	Data gap, no study on file
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, possible adverse effects
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
All record numbers through 993548 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T030707. Prepared by Gee, 3/27/92 based on reviews by J. Wong and J. Remsen(Gee) in 1985. Update: J. Kishiyama and Gee, July 7, 2003.
Note: There are three related compounds in the technical grade material. These are

5-hydroxymethoxymethyl-1-aza-3,7-dioxabicyclo (3.3.0) octane, SB 950 # 109, Chemical code # 1965; 5-hydroxymethyl-1-aza-3,7-dioxabicyclo (3.3.0) octane, SB 950 # 706, Chemical code # 1966 and 5-hydroxypoly[methyleneoxy(74% C2, 21% C3, 4% C4, 1% C5] methyl-1-aza-3,7-dioxabicyclo(3.3.0) octane, SB 950 # 707, Chemical code # 1967. The studies on file were conducted with the mixture (Nuosept 95) so all have the same data on file.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

Data gap, no study on file.

Subchronic:

50290 - 003 993542 Sasmore, D. P. and C. A. Tyson. "Effect of Nuosept 95 in Rats, 90-day Toxicity Study." SRI International, SRI Project LSC-8654, February 6, 1980.) Nuosept 95, lot 005-267, purity 50% active ingredients, was administered in the drinking water at average analytical doses of 0, 13, 62, or 245 mg/kg for 91 days to 20 Sprague-Dawley rats/sex/group. Constant drinking water concentrations were 0, 125, 625 and 3125 ppm which were predicted to yield doses of 0, 20, 100 and 500 mg/kg/day, based on 40 g water per day/rat and an average body weight of 250 g with Nuosept at 50% active ingredients. Reduced body weight and bodyweight gain for the high dose groups and reduced water consumption affected the actual doses consumed. Hematology parameters, urinalysis and ophthalmology were not affected by treatment. There were some serum chemistry alterations for both mid and high-dose groups, such as a decrease in alkaline phosphatase (both sexes), increase in BUN (high dose males), and a decrease in cholesterol (high dose females). No treatment-related histopathological changes were reported. No individual data were included in the report. NOEL = 13 mg/kg/day (based on a decrease in water consumption, which may have been related to taste) . UNACCEPTABLE (no individual data.) Upgradeable. (Kishiyama and Gee, 7/2/03).

CHRONIC TOXICITY, DOG

Data gap, no study on file.

SUBCHRONIC TOXICITY, RABBIT DERMAL

50290 - 010 115611 Elliot, P. H., A. E. Street, W. A. Gibson, P. A. Mullins, C. P. Cherry, and C. Gopinath. "Twenty-one Day Dermal Toxicity Study in Rabbits with Nuosept 95/Nuosept C." (Huntingdon Research Centre, England, NDX 1/84955/SB, January 21, 1985.) Nuosept 95 (purity not stated, lot no 84-11, sp. gravity of 1.137) was applied once/day to the shaved skin of 5 New Zealand White rabbits/sex/group at doses of 0, 100, 300, or 1000 mg/kg, for 6 hours/day for 21 consecutive days. Doses were based on Nuosept 95 as supplied with the % v/v being 10, 30 and 100% with increasing dose, applied at 0.88 ml/kg/day. Dermal irritation incidence and severity was dose related. NOEL = <100 mg/kg/day. Treatment- related decrease in alkaline

phosphatase was reported for the high dose group. There was a slight trend for reduced body weight change and food consumption for the high dose group. UNACCEPTABLE (composition of the test material needs confirmation). Upgradeable. (Kishiyama and Gee, 7/1/03)

ONCOGENICITY, RAT

Data gap, no study on file.

ONCOGENICITY, MOUSE

Data gap, no study on file.

REPRODUCTION, RAT

Data gap, no study on file.

TERATOLOGY, RAT

** 50290 - 010 115612 Smith, J. A., R. E Masters, D. M. John, and J. M. Offer. "A Study of the Effect of Nuosept 95 on Pregnancy of the Rat." (Huntingdon Research Centre Ltd., England, HRC Report No.: NDX 3/88962, November 14, 1988.) Nuosept 95 (purity 50.38%, batch no. 006-097-597) at doses of 0, 100, 300, or 1000 mg/kg was applied once/day to the skin of 25 Sprague-Dawley [CrL: COBS CD (SD) VAF+] mated female rats/group days 6 through 15 of gestation. The Nuosept 95 was applied neat with the volume adjusted for each dose. A slight but dose related retarded bodyweight gain was noted in the treated groups. Skin irritation (erythema, edema and scabbing) was seen in all treatment groups with severity increasing with dose. Dermal NOEL <100 mg/kg/day. Enlargement of axillary lymph nodes was noted with Nuosept 95 at 300 mg/kg (1/25) and 1000 mg/kg (2/25). Developmental NOEL $\geq$1000 mg/kg/day. ACCEPTABLE. (Kishiyama and Gee, 7/1/03).

TERATOLOGY, RABBIT

Data gap, no study on file.

GENE MUTATION

** 50290-003 993543 Haworth, S. R. "Salmonella/mammalian-microsome plate incorporation mutagenesis assay." (SRI International, study #601-257-1, 4/16/79) Nuosept 95 (lot 005-267, purity 50% - see 993542) was tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation, at 0.01, 0.05, 0.23, 0.45 or 0.9 µl/plate, triplicate plates. At 0.9 µl, with and without activation, there was a notable decrease in colonies indicating toxicity. No conclusive evidence of an increase in reversion rate. Originally evaluated as unacceptable (no purity of test article) but possibly upgradeable with description of the material tested. Wong, 4/10/85. The purity/composition of lot 005-267 is described in record 993542, thereby upgrading the study to ACCEPTABLE status. (Gee, 7/2/03).

50290-007 35478 is a duplicate of 993543.

50290-003 038438 [initially reviewed as 993543-2] "Mutagenicity studies of Nuosept 95." (D. van Goethem, Midwest Research Institute, project no. 4754-B, 6/25/79) Nuosept 95 in water (purity not known, lot no. 005-267) was tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 at 0, 5, 10, 50, 100 and 250 in the first assay and at 375, 500, 625 and 750 μg/plate in a second assay, with and without activation from Aroclor-induced rats. Protocol states there were to be duplicate plates. No evidence of mutagenicity reported. UNACCEPTABLE (no description of the test article, no individual plates, inadequate methods section) Wong, 4/10/85
Note: The composition of Nuosept 95, lot 005-267 is given in 993542 so that deficiency is resolved. The others remain. (Gee, 7/2/03)

CHROMOSOME EFFECTS

** 50290-003 993544 Rushbrook, C. J. and T. A. Jorgenson "Dominant lethal study of Nuosept 95." (SRI International, Project LSC-8654, 12/79) Nuosept 95 (lot 005-267, 50% inerts) was given to male Sprague-Dawley rats in drinking water with 11 males per group at 0, 125, 625 or 3125 ppm (based on the 50% active ingredients) with TEM as positive control. Overall average daily doses were 14, 66 and 268 mg/kg/day of Nuosept 95. Water intake was lower by approximately 30% at the high dose. Following the ten-week treatment period, each male was mated with 2 untreated females for 7 days. The males were mated for a second week with new females. No statistically significant effect was observed except with TEM, the positive control. ACCEPTABLE. Wong, 4/10/85. Revised by Gee, 7/2/03.

50290-007 35476 is a duplicate of 993544 in 003.

50290-003 993545 Evans, E. L. "Effect of Nuosept 95 in rats: Cytogenetic evaluation of bone marrow cells." (SRI International, project LSC-8654, 2/80) Nuosept 95 (no purity stated) was given in drinking water to male Sprague-Dawley rats for 13 weeks with 6 per group at 0 and 20 mg/kg, 8 males at 100 mg/kg and 10 at 500 mg/kg. Bone marrow cells were examined for aberrations for 5 males of the negative and positive (TEM) controls and 500 mg/kg groups only. Fifty cells per animal were scored for chromosome number and aberrations. No effect was reported. UNACCEPTABLE (use of one sex only without justification, only one dose examined, too few total number of animals examined, no purity of test material - not upgradeable). Wong, 4/10/85.
Note: These animals were part of the 90-day study - see 993542. The test article was 50% active ingredients from lot 005-267. That report contains the statement that since no effects were seen at the high dose, the lower doses were not analyzed. The lack of justification for examining only males. The study could possibly be upgraded with a justification. Revised by Gee, 7/2/03.

50290-007 35477 is a duplicate of 993545 in 003.

DNA DAMAGE

**** 50290-003 993546** Haworth, S. R. "Bacterial DNA damage/repair suspension assay."

(EG&G Mason Research Institute, MD, Study No. 026-601-257-6, 8/3/79) Nuosept 95 (lot 005-267, no purity stated) was tested with E. coli strains WP2uvrA recA$^+$ and WP100uvrA$^-$recA$^-$ and with Salmonella strains TA1978uvrB$^+$ and TA1536uvrB$^-$at 0, 0.03, 0.3, 0.6 or 0.9 µl/plate in triplicate, with and without activation. The cells were incubated for 90 minutes with shaking in a volume of 1 ml. At termination, 100 µl were plated in top agar and incubated for 48 hours. There was preferential killing of the repair deficient strains of E. coli and of Salmonella when compared with the repair proficient strains. Possible adverse effect. Initially reviewed as unacceptable by Wong, 4/10/85. Rereviewed as a duplicate submission in 50290-007 by Gee, 10/3/85 and concluded to be ACCEPTABLE - see supplemental worksheet.
Note: Purity of lot 005-267 is given in record 993542 as 50% active ingredients, satisfying that deficiency. (Gee, 7/2/03)

50290-007 35479 is a duplicate of 993546 in 003.

50290-003 38439 [initially reviewed as 993546-2] Van Goethem, D. "Bacterial DNA repair assay of Nuosept 95." (Midwest Research Institute, Missouri, MRI project no. 4822-B, 10/31/79) Nuosept (lot 005-267, purity not stated) was dissolved in water and assayed at 0, 50, 100, 500, 1000 and 5000 µg/ml of bacterial suspension. Bacteria were E. coli strains W3110 (pol A$^+$) and p. 3478 (polA$^-$) and Salmonella strains TA1978uvrB$^+$ and TA1536uvrB$^-$. The assay was performed with and without rat liver activation. Both the disc and the suspension methods were used. For the suspension, bacteria were at 10^4 in 1 ml with 0.1 ml of test material added and incubated for 1 hour. At termination, 0.1 ml was plated on agar plates in duplicate. After 18 hour, colonies were counted. For disc method, 5, 10, 50, 100 or 500 µg/plate was added to a 1.0 cm filter paper. The zone of inhibition was measured. Both assays indicated a preferential killing of the repair deficient strains. Activation was not necessary for the activity. Possible adverse effect. UNACCEPTABLE (purity not included, no individual plate counts) Possibly upgradeable. Wong, 4/10/85 and Gee, 10/3/85.
Note: The purity of lot 005-267 is given in record 993542 as 50% active ingredients. (Gee, 7/7/03)

50290-007 37178 a duplicate of 38439 on 003.

50290-003 993547 Myhr, B. C., study director. "Evaluation of Nuosept 95 in the primary rat hepatocyte unscheduled DNA synthesis assay." (Litton Bionetics, project no. 20991, 8/80) Nuosept 95 (lot and purity not included) was tested with hepatocytes from a male Fischer rat. Concentrations were 0, 0.0156, 0.0313, 0.0625, 0.125, 0.25, 0.5, 1.0 and 2.0 µl/ml in medium. Incubation time was 1 hour followed by three additional hours with ^{3}H-thymidine. Cytotoxicity was determined at 2 and 24 hours after treatment. Possible adverse effect - increased % of cells with 6 or more grains at 0.0625 (32.3%) and 0.125 (25.3%) µl/ml with good viability. UNACCEPTABLE (no purity of the test material, net nuclear grains in medium control was 2.05 with 11% having $\geq$ 6 grains, only the averages are in the report) Wong, 4/10/85 and Gee, 10/3/85.

50290-007 035480 is a duplicate of 993547 in 003.

50290-003 993548 Thilagar, A., study director. "An evaluation of carcinogenic potential of Nuosept 95 employing the C3H/10T1/2 cell transformation assay." (ER&G Mason Research Institute, study no. 601-257-8, 9/17/79) Nuosept 95 (no purity stated, lot 005-267) was tested at 0, 0.0005, 0.001, 0.002 and 0.004 µl/ml, 12 plates per concentration, 18 hours of exposure. Four parallel plates were used to determine cytotoxicity. Plates were scored for foci 36 days after

treatment with Types I, II and III scored. The results suggest an increase in Type II and III foci with treatment. Possible adverse effect. There were no foci recorded in the medium control, one Type III and 2 Type II at 0.001 µl/ml, one Type II in each of 0.002 and 0.004 µl/ml. UNACCEPTABLE (no activation included, purity not included) Not upgradeable. Wong, 4/10/85 and Gee, 10/3/85.
Note: The purity of lot 005-267 is given in record 993542 as 50% active ingredients. (Gee, 7/7/03)

50290-007 35481 is a duplicate of 993548 in 003.

50290-003 38440 [initially reviewed as 993548-2] Schechtman, L. M., study director "Activity of T 1597 in an in vitro mammalian cell transformation assay in the absence of exogenous metabolic activation." (Microbiological Associates, 4/21/80) Nuosept 95 (lot 005-267, no purity) was tested with C3H 10T1/2 clone 8 mouse embryo cells without activation at concentrations of 0, 0.003, 0.001 and 0.0003 µl/ml for 20-24 hours with 12-15 dishes per concentration. Cells were plated at 250/dish for cytotoxicity and at 1 x 10^3 for transformation assay. 3-MC was the positive control. No Type II or III foci were see in the dishes exposed to Nuosept 95 or medium control. 3-MC was effective. No adverse effect was noted. UNACCEPTABLE (no activation included, no purity of test article, summary data only in Table II) Not upgradeable. Wong, 4/10/85.
Note: Purity of lot 005-267 is given in record 993542 as 50% active ingredients. (Gee, 7/7/03).

50290-007 35638 is a duplicate of 38440 in 003.

50290-003 38441 [initially reviewed as 993548-3] Thilagar, A., study director. "An evaluation of carcinogenic potential of R-1162 employing the C3H/10T1/2 cell transformation system." (EG&G Mason Research Institute, study no. 26-205-435-8, 7/21/80) R-1162 (no further information of lot no, purity or composition) was tested to determine if it caused cell transformation at concentrations of 0, 0.0098, 0.0195, 0.039 and 0.078 µl/ml, 18 hour treatment. DMBA was the positive control. No transformed foci were found in the experimental dishes (12 per concentration). DMBA was effective. No adverse effect reported. UNACCEPTABLE (test article not defined, no activation included) Wong, 4/11/85.

50290-007 35639 is a duplicate of 38841 in 003.

50290-003 38442 [initially reviewed as 993548-4] Thilagar, A., study director. "An evaluation of carcinogenic potential of R-1143 employing the C3H/10T1/2 cell transformation system." (EG&G Mason Research Institute, study no. 026-205-437-8, 7/21/80) R-1143 (no further information of lot no, purity or composition) was tested at 0, 0.0006, 0.0012, 0.0024 and 0.0048 µl/ml, 18 hour exposure without activation only. DBMA was the positive control and was effective. No transformed foci were found in the experimental dishes (12 per concentration). No adverse effect reported. UNACCEPTABLE (test material was not described, no activation was included) Not upgradeable. Wong, 4/11/85.

50290-007 35640 is a duplicate of 38442 in 003.

51922 - 001 121734 Hamilton, C. M., study director. "Measurement of Unscheduled DNA Synthesis in Male Fischer-344 Rat Hepatocytes Following In Vivo Treatment with Nuosept 95." (SRI International, Report # LSC 4084-U01-92, 8 March 1993). Nuosept 95 (purity not given, lot no. 05249587, clear liquid) was used as the test article. Three male Fischer 344 rats per

group received a single treatment of the test material by gavage at 0 (water), 875, 1750, or 3500 mg/kg. Animals were sacrificed for primary hepatocytes at 2 and/or 16 hours after treatment. Dimethylnitrosamine was the positive control. One death occurred at 3500 mg/kg. Rats in the mid and high dose groups exhibited "rough" fur on the morning after dosing. Three slides were prepared per animal and 30 cells per slide were scored for grain counts and the percent of cells in repair. There was no induction of unscheduled DNA synthesis. UNACCEPTABLE and upgradeable with submission of test article and dosing material characteristics. (H. Green and Gee, 6/30/03).

NEUROTOXICITY

Not required at this time.